

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-711**

**APPROVABLE LETTERS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-711

Epix Medical, Inc.  
Attention: Robert A. Morgan  
Executive Director, Regulatory Affairs and Quality  
71 Rogers Street  
Cambridge, MA 02142

Dear Mr. Morgan:

Please refer to your new drug application (NDA) dated December 12, 2003, received December 15, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasovist (Gadofosveset) Injection.

We acknowledge receipt of your submissions dated May 23, July 13, August 1 and 24, September 1, and October 10, 2005.

Although your May 23, 2005 submission included responses to deficiencies identified in our January 12, 2005 action letter, you did not provide the data requested in that letter. However, we determined that the May 23, 2005 submission still constitutes a complete response to our January 12, 2005 action letter.

We completed our review of this amended application, and it is approvable. However, before the application may be approved, it will be necessary to address the following clinical deficiencies.

Gadofosveset efficacy has not been adequately demonstrated. As communicated in our January 12, 2005 letter, "there is a lack of substantial evidence to conclude that the sensitivity and specificity of gadofosveset-enhanced magnetic resonance angiography (MRA) is superior to that of non-contrast MRA." In the same letter, we advised the following: "you will need to conduct adequate and well-controlled clinical studies that demonstrate superior efficacy for gadofosveset MRA in the vascular region(s) for which you are seeking indication(s). One of the requested new studies could be a blinded re-read of images from Study MS-325-12 and Study MS-325-13 combined using pre-specified criteria for selecting and interpreting baseline images. If positive, one additional confirmatory study may suffice to support an indication for gadofosveset MRA in aortoiliac disease.

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Our January 12, 2005 approvable letter was based on a determination that although efficacy had not yet been adequately demonstrated, there was reasonable likelihood that this could be accomplished by performing the additional requested studies. The submitted exploratory statistical analyses of imputation schemes for uninterpretable radiographic examinations are not acceptable substitutes for

the proposed new studies. The submission also provides an exploratory efficacy analysis of patient subgroups defined by specific settings on the imaging platforms. These post-hoc analyses explore (1) the projected outcome that might have occurred if large imbalances in the number of uninterpretable scans between the investigational and comparator arms did not exist and (2) the impact of the failure to adhere to standard imaging methods on the efficacy outcome. These analyses do not address the deficiencies inherent in the image acquisition, namely the lack of validation of image quality at baseline before administration of contrast, and the lack of a provision for repeating scans found to be suboptimal. The analyses also do not address the validation of blinded reader training. These exploratory analyses cannot overcome the inherent flaw due to lack of standardization and validation of the imaging protocols.

As an exploratory analysis, we evaluated the diagnostic performance of each of the three blinded readers on images that at least one other reader classified as "uninterpretable". Each reader's performance on this subset of images was similar to his overall performance on the interpretable images. This analysis suggests that a judgment of uninterpretable for baseline images might not be attributable to the image's intrinsic properties but rather to suboptimal training of the blinded readers. FDA's analysis provides evidence that more rigorous reader training (focused on variation in image quality from different clinical sites, artifact identification, anatomic variation, and application of contextual diagnosis using clues from adjacent vessel segments) would probably reduce the number of uninterpretable scans. A re-read of the images by new appropriately trained blinded readers will likely result in a substantial reduction in the proportion of uninterpretable images.

The present submission also proposes that the efficacy of gadofosveset be judged based on performance criteria that were either not pre-specified or were specified as secondary endpoints in the phase 3 studies. You will need to pre-specify the criteria for gadofosveset clinical utility before the start of new studies or before re-read of the blinded images.

As previously communicated, new studies (possibly including a blinded reread of images from those studies) demonstrating the safety and efficacy of gadofosveset for the proposed indication will be required. Any future resubmission which does not provide data from the requested new studies will likely be considered incomplete and/or result in a determination that the application is not approvable.

In order to resolve the deficiencies with this application, we request that you submit all information requested in our January 12, 2005, letter. This includes:

- Data from new studies, as previously requested (see above quote). Please refer to the January 12<sup>th</sup> letter for information regarding issues that should be clearly addressed in the protocols.
- A current safety update as described at 21 CFR 314.50(d)(5)(vi)(b) and in items 1 – 7 of our prior letter.
- Updated draft labeling.

We encourage you to request a meeting with the Division of Medical Imaging and Hematology Products to discuss in detail the design of clinical studies that might be used to support approval of gadofosveset. You may also request Special Protocol Assessment for your proposed studies, including the protocol and statistical analysis plan for the reread study, as described in the FDA "Guidance for Industry: Special Protocol Assessment" available at <http://www.fda.gov/cder/guidance/3764fnl.htm>.

Labeling comments are deferred at this time. Please submit updated draft product labeling with your resubmission.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Medical Imaging and Hematology Drugs to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

*{See appended electronic signature page}*

Karen Weiss, M.D.  
Deputy Office Director  
Office of Oncology Drugs  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Karen Weiss  
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Karen D. Weiss



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-711

Epix Medical, Inc.  
Attention: Robert A. Morgan  
Executive Director, Regulatory Affairs and Quality  
71 Rogers Street  
Cambridge, MA 02142

Dear Mr. Morgan:

Please refer to your new drug application (NDA) dated December 12, 2003, received December 15, 2003, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vasovist™ (Gadofosveset Trisodium) Injection 0.25mmol/mL.

We acknowledge receipt of your submissions dated January 30, February 6, 10, 23, and 27, March 10, 11, 12, and 30, April 14, May 14, June 3, 11, and 29, July 16, August 6, 11, 12, 19, 20, 30, September 1, 2, 8, 10, 14, 15, 28, October 1, 6, 11, 12, 13, 22, 27, December 1 and 29, 2004, and January 5, 2005.

We have completed our review of this application and it is approvable under 21 CFR 314.125(b). Before this application may be approved, it will be necessary for you to address the following clinical deficiency:

1. There is a lack of substantial evidence to conclude that the sensitivity and specificity of gadofosveset-enhanced magnetic resonance angiography (MRA) is superior to that of non-contrast MRA.

Your phase 3 studies of gadofosveset suggest improvement in sensitivity and specificity for gadofosveset-enhanced images compared to non-contrast baseline MRA images for aortoiliac

The protocol-specified analyses for these studies impute an incorrect diagnosis for baseline images containing uninterpretable vessels. We are concerned that a lack of standardization in the baseline imaging procedures used across study sites resulted in relatively high baseline uninterpretable rates in your phase 3 studies.

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At the Division's request, you have performed several alternative analyses using different imputation schemes for baseline uninterpretable images. One of these schemes, interpretables alone, in which only baseline and enhanced images with interpretable vessels were used, is commonly performed in imaging studies (see e.g., Perreault et al., *Radiology* 229:811-820, 2003). Arguably, this represents a conservative analysis, but in our view provides the least biased look at the data. Using this scheme, improved sensitivity and specificity were demonstrable for only one reader in one of the aortoiliac studies (Study MS-325-12) [

] Moreover, when the two similarly designed aortoiliac studies are compared, improved specificity was demonstrated for two readers in Study MS-325-12, whereas improved sensitivity was demonstrated for all readers in Study MS-325-13.

You have argued that considering all the possible imputation schemes, results from the two phase 3 aortoiliac studies taken together with the phase 2 Study MS-325-09 could suggest "larger changes in sensitivity with modest or no changes in specificity" (Epix Medical submission dated December 29, 2004). We do not find this suggestion to be supported by the phase 2 study however. In that study, also conducted in patients with known or suspected aortoiliac disease, sensitivity with gadofosveset dosed at 0.03 mmol/kg increased 17-25% across readers and specificity increased 15-32% across readers over baseline. The apparent lower specificity observed for gadofosveset-enhanced imaging in your phase 3 aortoiliac studies is not well explained. Again, it is possible that the relatively high baseline uninterpretable rate in the phase 2 study may have biased the results in favor of gadofosveset. To conclude, while the results obtained from the various imputation schemes demonstrate hints of efficacy, we believe that clear-cut superiority in sensitivity and specificity for gadofosveset MRA has not been demonstrated for any vascular region.

The following information is needed to address this deficiency:

You will need to conduct adequate and well-controlled clinical studies that demonstrate superior efficacy for gadofosveset MRA in the vascular region(s) for which you are seeking indication(s). One of the requested new studies could be a blinded reread of images from Study MS-325-12 and MS-325-13 combined using pre-specified criteria for selecting and interpreting baseline images. If positive, one additional confirmatory study may suffice to support an indication for gadofosveset MRA in aortoiliac disease. [

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Protocols for newly planned clinical studies should clearly address the following: (1) standardization of baseline imaging procedures across study sites, (2) evaluation of the adequacy of baseline images prior to gadofosveset imaging, including provision for a repeat baseline image if it was found to be inadequate or uninterpretable, (3) training of readers, (4) quality assurance to ensure protocol compliance across sites, and (5) separate evaluation of dynamic and steady-state images. A prospectively-defined imputation scheme for uninterpretable images that is neutral to the drug product should be utilized. We believe studies should be sufficiently powered to show at least a 10% difference in sensitivity and specificity for gadofosveset-enhanced images over non-contrast images, and that the sensitivity and specificity of enhanced images should be at least 80%. Comprehensive safety monitoring should be performed, including baseline and follow-up measurement of hematologic

parameters and electrolytes. Abnormal laboratory values should be followed until full recovery. Sufficient numbers of patients with renal impairment should be enrolled to assess the magnitude, time to onset and recovery of laboratory abnormalities relative to patients with normal renal function.

You may request special protocol assessment for your proposed phase 3 study protocols, including the protocol and statistical analysis plan for the reread study. The Division will evaluate specific protocols and work toward agreement with you on the design of clinical studies that can be used to support approval of gadofosveset.

Labeling comments are deferred at this time. Please submit updated draft product labeling with your resubmission.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the

application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Medical Imaging and Radiopharmaceutical Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact CAPT James Moore, Regulatory Project Manager, at (301) 827-6254.

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.  
Deputy Office Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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Julie Beitz

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